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    (FILE 'HOME' ENTERED AT 17:20:39 ON 01 NOV 2004)

    FILE 'STNGUIDE' ENTERED AT 17:20:47 ON 01 NOV 2004

    FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 17:20:58 ON
    01 NOV 2004
                E MAJEED MUHAMMED/AU
L1           41 S E2-E4
L2            3 S L1 AND BOSWEL?
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L3          127 S E3
L4            2 S L3 AND BOSWEL?
                E HUANG MOU/AU
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L6            4 S L5 AND BOSWEL?
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L10          15 S L9 NOT PY>=2000

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on STN

CCESSION NUMBER: 1999206199 EMBASE

ITLE: [Salai Guggal - Indian incense for therapy of rheumatoid arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER RHEUMATOIDEN ARTHRITIS.

UTHOR: Trubestein G.

ORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad Orb, Germany

OURCE: Biologische Medizin, (1999) 28/3 (121-124).
Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA

OUNTRY: Germany

OCUMENT TYPE: Journal; General Review

ILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index

ANGUAGE: German

UMMARY LANGUAGE: English; German

B Salai Guggal, the gum resin of **Boswellia** serrata, has been used since a long time as a traditional remedy in Ayurveda medicine in India for inflammatory diseases such as rheumatoid **arthritis**, ulcerative colitis and **Crohn**'s disease. Compounds from the gum with genuine antiinflammatory effect are the **boswellic** acids. **Boswellic** acids inhibit the leukotriene biosynthesis. The effect is triggered by **boswellic** acids binding the enzyme. In clinical studies in Europe with Salai Guggal promising results were found in patients with rheumatoid **arthritis**. Besides the preparations from India and Switzerland with 400 mg dry extract products of Olibanum are used as Olibanum guttae and Olibanum RA ointment and other homoeopathic preparation.

ANSWER 12 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER: 2002:658137 CAPLUS
CUMENT NUMBER: 137:190761
TLE: Water soluble boswellic acids, their preparation and use for treating inflammatory conditions
VENTOR(S): Majeed, Muhammed; Badmaev, Vladimir
TENT ASSIGNEE(S): Sabinsa Corporation, USA
URCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
CUMENT TYPE: Patent
NGUAGE: English
MILY ACC. NUM. COUNT: 1
TENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066491	A1	20020829	WO 2002-US3384	20020215

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IORITY APPLN. INFO.: US 2001-268713P P 20010215

10/076,667 abandoned

3 A new composition, which can be formed through a method comprising: (a) dissolving mixts. of **boswellic** acids in a water and alc. solution to form a mixture; (b) adding one or more alkali salts to the mixture to form a salt solution; (c) filtering the solution to sep. un-reacted alkali salt from a filtrate; and (d) recovering the soluble **boswellic** acid mixture from the filtrate, is described. Addnl., the new composition can be formed by using super critical carbon dioxide. The new composition can be used to alleviate numerous inflammatory conditions, including, but not limited to, rheumatoid **arthritis** and osteoarthritis, colon cancer, prostate cancer and breast cancer, and a broad range of neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. The composition can be administered parenterally, orally, or topically.

STIC-ILL

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From: Jiang, Shaojia
Sent: Monday, November 01, 2004 6:11 PM
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L9 ANSWER 38 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1996:491734 CAPLUS
DOCUMENT NUMBER: 125:185262
TITLE: Anti-inflammatory actions of boswellic acids
AUTHOR(S): Singh, G. B.; Singh, Surjeet; Bani, Sarang
CORPORATE SOURCE: Regional Research Laboratory, Department Pharmacology, Jammu Tawi, 180 001, India
SOURCE: Phytomedicine (1996), 3(1), 81-85
CODEN: PYTOEY; ISSN: 0944-7113
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

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ACCESSION NUMBER: 1999206199 EMBASE
TITLE: [Salai Guggal - Indian incense for therapy of rheumatoid arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER RHEUMATOIDEN ARTHRITIS.
AUTHOR: Trubestein G.
CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad Orb, Germany
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Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

ACCESSION NUMBER: 2001:447633 CAPLUS
DOCUMENT NUMBER: 135:220902
TITLE: Anti-tumor and anti-carcinogenic activities of triterpenoid, .beta.-boswellic acid
AUTHOR(S): Huang, Mou-Tuan; Badmaev, Vladimir; Ding, Yu; Liu, Yue; Xie, Jian-Guo; Ho, Chi-Tang
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy,

Gustav Trübestein

Salai Guggal – Indischer Weihrauch zur Behandlung der rheumatoiden Arthritis

Zusammenfassung

Salai Guggal, das Harz des indischen Weihrauchbaums, wird in Indien in der traditionellen Medizin (Ayurveda) seit langem zur Behandlung von entzündlichen Erkrankungen wie der rheumatoiden Arthritis, Colitis ulcerosa und Morbus Crohn eingesetzt. Inhaltsstoffe des Weihrauchs, die an der entzündungshemmenden Wirkung beteiligt sein dürften, sind Boswelliasäuren; diese führen zu einer Hemmung der Leukotrien-Biosynthese. Die Wirkung erfolgt nach Bindung von Boswelliasäuren an das Enzym.

Klinische Untersuchungen in Europa mit dem Harz des indischen Weihrauchbaumes erwiesen sich als wirksam bei der rheumatoiden Arthritis. Neben den handelsüblichen Präparaten aus Indien und der Schweiz mit 400 mg Trockenextrakt werden Weihrauchprodukte auch als Olibanum RA Tropfen und Olibanum RA Salbe und anderen homöopathischen Zubereitungen gegeben.

Schlüsselwörter: Boswelliasäuren, chronische rheumatoide Arthritis, Leukotriene, Weihrauch

Einleitung

Die Verwendung von Weihrauch (Olibanum) ist eng mit der kulturgeschichtlichen Nutzung von Geruchsstoffen und Räucherwerk für kultische und hygienische Zwecke verbunden. Im klassischen Altertum unseres Kulturkreises nahm die Bedeutung der natürlichen Harze des Weihrauchbaumes (Olibanum) aus dem arabischen Raum stark zu.

Das primäre Verbreitungsgebiet des Weihrauchbaumes umfaßt im wesentlichen Somalia, Nubien, Südarabien, Äthiopien und Teile des tropischen Afrika (Olibanum) sowie insbesondere Indien (Salai Guggal).

Das Harz des indischen Weihrauchbaums (Salai Guggal) wird in der traditionellen indischen Medizin (Ayurveda) seit Jahrtausenden eingesetzt, insbesondere bei entzündlichen Erkrankungen wie rheumatoider Arthritis und Osteoarthritis sowie auch bei zervikaler Spondylosis deformans. Die Applikation erfolgt in Form von Salben, Extrakten und Pulvern (5, 12, 13, 14). Im wesentlichen handelt es sich hierbei um das Gummiharz von Boswellia serrata Roxb. Die Menge, die jährlich von einem Baum in Indien gewonnen werden kann, wird auf zirka 1 kg geschätzt (12, 13). Die jährliche Ernte an indischem Weihrauch liegt über 1 000 Tonnen.

Hauptbestandteile dieses Gummiharzes sind neben Boswellia serrata Roxb. ätherische Öle, Terpinole, Arabinose, Xylose, Galaktose, Galakturonsäuren, Beta-Sitosterin und Phlobaphene.

Eine exakte Zuordnung der handelsüblichen Weihrauchsorten zu ihrer botanischen Herkunft ist oft nicht möglich, zumal der Weihrauch häufig in gemischter Form auf den Markt gelangt. Eine nachvollziehbare Qualitätskontrolle für die medizinische Anwendung ist unter diesen Umständen äußerst schwierig, obwohl sie notwendig wäre. Darüber hinaus sind die Harze des Weihrauchs (Olibanum) und des indischen Weihrauchs (Salai Guggal) klassische pflanzliche Vielstoffgemische mit den entsprechenden Eigenheiten in Qualitätssicherung, Forschung und Anwendung (17). Bislang sind jeweils mehr als 200 Inhaltsstoffe im Harz des Weihrauchs (Olibanum) identifiziert worden (13, 14, 19). Es ist anzunehmen, daß die Verhältnisse bei dem indischen Weihrauch vergleichbar komplex sind.

Wirkungsmechanismus

Indischer Weihrauch hemmt nach den vorliegenden Untersuchungen konzentrationsabhängig die Synthese von Leukotrienen (11). Die Ergebnisse von Ammon legen die Vermutung nahe, daß die azetylierten Boswelliasäuren des Weihrauchbaumes in der Arachidonsäurekaskade die Bildung von Leukotrienen hemmen (1, 2). Ein antioxidativer Effekt – wie bei anderen bekannten Hemmstoffen der Leukotrienbiosynthese – konnte nicht gefunden werden (3).

Über die Hemmwirkung auf die Leukotrienbiosynthese hinaus wurde in der Zwischenzeit auch berichtet, daß Boswelliasäuren, allerdings in wesentlich höheren Konzentrationen, in vitro auch die Proliferation von Tumorzellen wie HL 60 und CCRF-CEM (7) Glioblastomzellen (4) und Melanomzellen (3) hemmen.

Leukotriene verfügen über eine Reihe von Wirkungen, von denen die meisten am Entzündungsgeschehen beteiligt sind.

Möglicherweise könnte eine Hemmung der Komplementaktivierung zu der antiinflammatorischen Wirkung beitragen (8, 10, 20).

Forschungsergebnisse

Experimentelle Forschung

In der experimentellen Forschung wurden unterschiedliche Fraktionen aus dem Gummiharz des Weihrauchbaumes verwendet, die jedoch im wesentlichen Boswelliasäuren enthielten (14, 15). Die experimentellen Untersuchungen mit dem Rohharz und seinen verschiedenen Extrakten und Fraktionen wie auch mit Boswelliasäuren weisen auf deutliche, dosisabhängige antiinflammatorische Wirkungen hin (3, 6, 16).

Summary

Salai Guggal, the gum resin of Boswellia serrata, has been used since a long time as a traditional remedy in Ayurveda medicine in India for inflammatory diseases such as rheumatoid arthritis, ulcerative colitis and Crohn's disease. Compounds from the gum with genuine antiinflammatory effect are the boswellic acids. Boswellic acids inhibit the leukotriene biosynthesis. The effect is triggered by boswellic acids binding the enzyme.

In clinical studies in Europe with Salai Guggal promising results were found in patients with rheumatoid arthritis. Besides the preparations from India and Switzerland with 400 mg dry extract products of Olibanum are used as Olibanum guttae and Olibanum RA ointment and other homoeopathic preparation.

Keywords: Boswellia resin, boswellic acids, leukotrienes, rheumatoid arthritis

Klinische Forschung

In der klinischen Forschung wurden vor allem die in Indien und in der Schweiz erhältlichen Präparate aus Salai Guggal in Tablettenform eingesetzt. Dementsprechend unterscheiden sich die experimentell und klinisch untersuchten Zubereitungen; dies erschwert die pharmakologische Beurteilung. Die hier angesprochenen Zubereitungen enthalten jedoch alle ein ausreichendes Gemisch aus Boswelliasäuren, so daß die experimentell mit Extrakten ermittelten Ergebnisse mit den klinischen vergleichbar sind.

Klinische Untersuchungen

Zur Beurteilung der therapeutischen Anwendungen mit Salai-Guggal-Gummiharz – im wesentlichen Boswellia serrata – liegen neben einzelnen Berichten und Beobachtungsserien einige kleinere, zumeist offene Studien vor. Zum Einsatz kamen Präparate aus Indien wie Sallaki-Tabletten, gewonnen aus dem Rohharz mit 200 mg oder 400 mg Trockenextrakt. Sie entsprechen den über einen Schweizer Kanton vertriebenen H15 Ayurmedica-Tabletten, die 400 mg Trockenextrakt Boswellia serrata enthalten.

Die Präparate wurden bei Patienten mit rheumatoider Arthritis, Patienten mit Colitis ulcerosa und Morbus Crohn sowie auch bei Patienten mit Hirntumoren, insbesondere bei tumor- und operationsbedingtem Ödem eingesetzt. Für die Beurteilung der Erfahrungen mit Salai Guggal aus Indien müssen allerdings auch Gesichtspunkte der traditionellen Krankheitslehre und Arzneimittelcharakterisierung (Ayurvedische Regulationslehre) mit berücksichtigt werden, um Fehlinterpretationen der Ergebnisse zu vermeiden (21).

Inhaltsstoffe	Prozent
Wasser	10–12
Harz	55–57
Gummi	20–23
ätherisches Öl	8–9
unlösliche Bestandteile	4–5

Tab.: Hauptinhaltsstoffe des Weihrauchs aus Boswellia serrata (aus: Kluge H, Fernando RC. Weihrauch und seine heilende Wirkung. Heidelberg: Karl F. Haug 1998)

Ergebnisse der klinischen Untersuchungen

Im Vordergrund der klinischen Untersuchungen standen in der Schweiz und Deutschland der Einsatz von Salai-Guggal-Gummiharz aus Boswellia serrata bei Patienten mit rheumatoider Arthritis. Die Ergebnisse kontrollierter Studien fielen unterschiedlich aus. 1994 wurden auf der Tagung der Deutschen Gesellschaft für Rheumatologie zwei plazebokontrollierte Doppelblindstudien bei Patienten mit langjähriger rheumatoider Arthritis vorgestellt, die unter einer Basistherapie unverändert entzündliche Aktivitäten aufwiesen. Über 12 Wochen wurde H15 Ayurmedica (ebi pharm, Kirchlindach/Schweiz) oder Plazebo gegeben (in der 1. Woche 1 200 mg/Tag, in den nachfolgenden 11 Wochen je nach Gruppenzuteilung 2 400 mg beziehungsweise 3 600 mg/Tag H15 Ayurmedica). Die Auswertung der Daten von 81 Patienten ergab, daß Gelenkschwellungen, Gelenkschmerzhaftigkeit, Morgensteifigkeit, Schmerzintensität und als laborchemischer Parameter die Blutkörperchensenkungsgeschwindigkeit (BSG) in der H15-Ayurmedica-Gruppe im Vergleich zu der Plazebogruppe vermindert waren. Auch war die Abbruchrate unter der H15-Ayurmedica-Medikation geringer als unter Plazebo (9). Eine 1998 publizierte Teilauswertung eines Zentrums mit 37 Patienten der multizentrischen Studie zeigte jedoch keine signifikanten oder klinisch bedeutsamen Unterschiede zwischen der H15-Ayurmedica-Gruppe und der Plazebogruppe bei den gewählten klinischen und serologischen Parametern (18).

Es kann somit festgehalten werden, daß

für H15 Ayurmedica (Trockenextract aus Boswellia serrata des indischen Weihrauchs) bei der rheumatoiden Arthritis erste, weitgehend noch unpublizierte Erfahrungen und kleinere Studien vorliegen.

Wertung der Ergebnisse

Bei der rheumatoiden Arthritis handelt es sich um ein von der Intensität der Beschwerden her stark wechselhaftes Krankheitsbild. Zur Behandlung der akuten Schmerzsymptomatik im Rahmen eines neuen Krankheitsschubs und zur Behandlung neu aufgetretener schmerzhafter Bewegungseinschränkungen ist der indische Weihrauch nach den bisher vorliegenden Untersuchungen nicht geeignet. Bei einem akuten Schub der rheumatoiden Arthritis haben nichtsteroidale Antirheumatika, Kortikosteroide und physiotherapeutische Maßnahmen die Priorität. Obwohl große und ausreichend lang durchgeführte kontrollierte Untersuchungen mit Salai-Guggal-Gummiharz aus Boswellia serrata noch fehlen, kann für die Langzeittherapie der rheumatoiden Arthritis diese Medikation in Betracht gezogen werden, da die Ergebnisse bei dieser Indikation vielversprechend sind.

Nebenwirkungen

Das Harz aus Boswelliaarten hat eine äußerst geringe Toxizität, Nebenwirkungen werden bei bestimmungsgemäßem Gebrauch nur in geringem Umfang beobachtet. Selten treten bei mit H15 Ayurmedica behandelten Patienten mit chronischer Polyarthritis und Spondylarthritis ankylopoetica gastrointestinale Beschwerden auf – auch nach eigenen Beobachtungen. Allergische Reaktionen sind nur vereinzelt beobachtet worden.

Verbreitung

Unter dem indischen Handelsnamen Sallaki werden Tabletten aus dem Rohharz angeboten, die 200 mg beziehungsweise 400 mg Trockenextrakt enthalten. Sie entsprechen den über einen Schweizer Kanton vertriebenen H15 Ayurmedica-Tabletten (Boswellia serrata). Das frühere Bundesgesundheitsamt (heute Bundesinstitut für Arzneimittel und Medizinprodukte) in Berlin hat vor einigen Jahren einen Antrag auf Zulassung des Weihrauchpräparates H15 in Deutschland für die Indikation rheumatoide Arthritis mangels hinreichender wissenschaftlicher Unterlagen abgelehnt.

Indikationen

Entsprechend den klinischen Erfahrungen, die zu einer Registrierung von H15 Ayurmedica im Halbkanton Appenzell / Außerrhoden der Schweiz führten, wird Salai-Guggal-Gummiharz aus Boswellia serrata bei rheumatoider Arthritis eingesetzt. Dabei ist festzuhalten, daß es sich bei der rheumatoiden Arthritis um ein von der Intensität der Beschwerden her stark wechselhaftes Krankheitsbild handelt. Zur Behandlung der akuten Symptome im Rahmen eines erneuten Krankheitsschubs und zur Behandlung neu aufgetretener Beschwerden ist der indische Weihrauch, auch nach den Herstellerangaben, nicht geeignet. H15 Ayurmedica kann jedoch für die Langzeittherapie der rheumatoiden Arthritis eingesetzt werden, zumal die Nebenwirkungsrate sehr gering ist. Weitere Indikationen für den indischen Weihrauch (Salai-Guggal-Gummiharz) wie Colitis ulcerosa und Morbus Crohn befinden sich in Abklärung.

Neben diesen Präparaten werden Weihrauchprodukte auch als homöopathische Urtinktur (z.B. Olibanum RA-Tropfen) und andere homöopathische Zubereitungen im Niederpotenzbereich ohne Angaben einer therapeutischen Indikation angeboten. Darüber hinaus wird Weihrauch auch als Nahrungsergänzungsmittel (z.B. Vita Weihrauchkapseln) vertrieben.

Vorgehen in der Praxis

Da der indische Weihrauch als Therapieprinzip durch die Laienpresse den Patienten bekannt geworden ist, wird der behandelnde Arzt von Patienten mit rheumatoider Arthritis häufiger auf diese Medikation angesprochen. So hat H15 Ayurmedica nicht nur in der Schweiz sondern auch in Deutschland eine größere Verbreitung gefunden, wobei in der Regel Tabletten zu 400 mg (Trockensubstanz) verordnet werden. Salai-Guggal-Gummiharz aus Boswellia serrata wird als Arzneimittel entweder aus Indien oder unter der Bezeichnung H15 Ayurmedica (Boswellia serrata) aus der Schweiz bezogen. Die Kosten für 100 Tabletten H15 Ayurmedica à 400 mg betragen zur Zeit bei Bezug aus der Schweiz ca. DM 100,– (unverbindliche Preisempfehlung des Importeurs). Als Dosierung werden zu Beginn der Therapie täglich 3mal 2 Tabletten à 400 mg, später 3mal 1 Tablette à 400 mg empfohlen. Nach den bisherigen Erfahrungen setzt die Wirkung des Weihrauchpräparates langsam ein, meist erst nach 4–6 Wochen. Eine Begleitmedikation zur Verminderung der Schmerzen des Patienten wird deshalb zu Beginn der Behandlung mit H15 Ayurmedica erforderlich sein.

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Anschrift des Verfassers
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D-63619 Bad Orb

AKTUELLER BERICHT

HOT – Hypertension Optimal Treatment: Größte abgeschlossene Hochdruck-Interventionsstudie

Die HOT-Studie wurde durchgeführt, um definitive Aussagen für eine optimierte Hochdruck-Therapie zu erhalten. Der Schlaganfall und die koronare Herzkrankheit sind die schwerwiegendsten Komplikationen der arteriellen Hypertonie. Die Empfehlungen nationaler und internationaler Gremien (Deutsche Hochdruck-Liga, JNC [Joint National Committee of Prevention] und WHO / ISH) haben als Zielkriterium einen diastolischen Blutdruck von unter 90 mmHg als erstrebenswert definiert, wobei der systolische Blutdruck auf Werte unter 140 mmHg gesenkt werden sollte.

Eine Metaanalyse von 14 Interventionsstudien aus dem Jahr 1990 an ca. 37 000 Patienten mit essentieller Hypertonie zeigte, daß das Schlaganfallrisiko unter einer antihypertensiven Therapie um ca. 40% abnimmt. Bei koronaren Ereignissen fand sich jedoch nur eine Reduktion um 12%. Mögliche Ursachen für die geringe Beeinflussung der koronaren Herzkrankheit durch eine antihypertensive Therapie sind offenbar die nicht ausreichende Behandlung weiterer Risikofaktoren; darüber hinaus war bisher nicht geklärt, ob der anzustrebende diastolische Blutdruck mit 90 mmHg diastolisch nicht zu hoch angesetzt war.

Um die Therapiesicherheit zu erhöhen, wurde die HOT-Studie nach dem Probe-Design (prospektiv, randomisiert, offen, mit verblindeter Bewertung der Zielkriterien) durchgeführt; nunmehr beendet ist sie die zur Zeit größte, abgeschlossene Hochdruck-Interventionsstudie.

Die HOT-Studie hatte folgende Zielparameter:

- Ausmaß der Reduktion in der kardiovaskulären Morbidität und Mortalität unter der antihypertensiven Therapie bei Patienten mit den angestrebten drei diastolischen Blutdruckwerten von ≤90 mmHg, ≤85 mmHg und ≤80 mmHg.
- Zusammenhang zwischen den erreichten Blutdruckwerten und dem Risiko der kardiovaskulären Morbidität und Mortalität.
- Senkung des Risikos von kardiovaskulärer Morbidität und Mortalität bei zusätzlicher Gabe von 75 mg ASS/Tag, verglichen mit Plazebo.

Methode

18 790 Patienten aus 26 Ländern mit einem Alter von 50–80 Jahren (im Mittel: 61,5 Jahre) mit einer Hypertonie und diastolischen Blutdruckwerten zwischen 100–115 mmHg (im Mittel: 105 mmHg) wurden in drei Gruppen mit anzustrebenden diastolischen Werten ≤90 mmHg, ≤85 mmHg und ≤80 mmHg randomisiert. Entsprechend diesen Zielparametern wurden folgende Gruppen gebildet:
bei 6 264 Patienten war der Ziel-Blutdruck ≤ 90 mmHg;

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ACCESSION NUMBER: 1996:491734 CAPLUS
DOCUMENT NUMBER: 125:185262
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CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad Orb, Germany
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AUTHOR(S): Huang, Mou-Tuan; Badmaev, Vladimir; Ding, Yu; Liu, Yue; Xie, Jian-Guo; Ho, Chi-Tang
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy,

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Anti-inflammatory actions of boswellic acids

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Summary

Boswellic acids (BA) demonstrated dose-related anti-inflammatory activity (AIA) in acute tests of carrageenan-, histamine- and dextran-induced edema in rats and mice. It elicited inhibitory action on vascular permeability in mice induced by acetic acid. Marked AIA was observed in chronic models of adjuvant-induced polyarthritis and formaldehyde arthritis in rats and bovine serum albumin-induced arthritis in rabbits. It produced significant protective effects in sodium urate gouty arthritis in dogs. BA reduced exudate volume and inhibited leucocyte migration in carrageenan-induced pleurisy in rats. It did not affect the parturition period in pregnant rats or castor oil-induced diarrhea in rats. It failed to exhibit any analgesic or ulcerogenic effects. BA elicited antipyretic activity in rats and rabbits. LD_{50} of BA was found to be greater than 2 g/kg in rats and mice when administered orally or intraperitoneally.

Key words: boswellic acid, anti-inflammatory activity in rats and mice, carrageenan-, histamin- and elextran induced edema tests, chronic arthritis models.

Introduction

Inflammation and various inflammatory disorders including rheumatoid arthritis are prevalent all over the world. They afflict large percentage of the world's population and are usually treated with chemical compounds that either inhibit synthesis of prostaglandins (PGs) *e. g.* salicylates or the formation of PGs and leukotrienes, *e. g.*, glucocorticoids. Both PGs and leukotrienes are important mediators of various inflammatory diseases and play vital roles in the development of rheumatoid arthritis and associated disorders. Among the currently available anti-inflammatory drugs, glucocorticoids are much more powerful than those compounds that act only by inhibiting prostaglandin synthesis.

It is well known that since rheumatoid arthritis is a chronic inflammatory disease it needs to be treated with anti-inflammatory drugs over a long period. But these drugs, glucocorticoids specially, produce severe adverse side effects limiting their prolonged use. Consequently, there is a need to develop anti-inflammatory agents that inhibit the synthesis of either leukotrienes alone or leukotrienes and PGs together without producing adverse effects.

Over the past decade we have been actively engaged in the research and development of new anti-inflammatory agents based on natural sources (Singh et al., 1984; 1986; 1987; 1992; 1993; 1994; Singh and Singh, 1994) that selectively inhibit without adverse effects the synthesis of leukotrienes alone (Ammon et al., 1991) or leukotrienes and PGs. As a result of this investigation an alcoholic extract of gum resin exudate of *Boswellia serrata*, which has been marketed in India under the brand name of Sallaki since 1982 with no reported side effects (Singh and Atal, 1986). This product based on our technology is also being marketed under the brand name H-15 in Switzerland. β-boswellic acid and their derivatives have been isolated as its active constituents and have been found to exert a selective inhibitory action on the formation of 5-lipoxygenase product leukotriene formation (Safayhi et al., 1992).

Materials and Methods

Materials: The boswellic acids (BA) fraction is a partially purified material of triterpene acids obtained from gum resin of the *Boswellia serrata*. The BA fraction is prepared by extracting *Boswellia serrata* gum resin with methanol (95%), removing the non-acidic constituents and precipi-

tating the acids then drying them into a fine powder (Singh et al., 1993).

Methods: Experiments were performed on male Charles Foster rats (110–150 g), Swiss albino mice (22–28 g) and Himalayan strain rabbits (1.5–2.5 kg) maintained at a room temperature of 25 ± 1 °C. Test drugs were freshly prepared in gum acacia (2% w/v) administered orally 1 h prior to induction of edema in acute tests and once daily in chronic tests. The paw volume of rats was measured with a volume differential meter model 7101 Ugo Basile (Italy). Data were analyzed statistically using Student's T test.

Carrageenan-induced edema in rats

Edema was induced in rats organized into groups of five by injecting 0.1 ml of carrageenan (1% w/v) solution in normal saline (0.9% NaCl w/v) beneath the plantar surface of the left hind paw (Winter et al., 1962). The paw volume was measured immediately and 4 h after the carrageenan injection.

Carrageenan-induced edema in adrenalectomised rats

Adrenalectomy was performed in rats (n=5) under anesthesia. Experiments were done after two days by injecting carrageenan as described above.

Histamine-induced edema in rats

0.1 ml of histamine (0.1% w/v) solution was injected into the hind limb of rats (Horakova and Muratova, 1964).

Dextran-induced edema in rats

0.1 ml of dextran (6% w/v) solution was injected into the subplantar region of the hind paw after 1 h after treatment with the drug (Winter, 1964).

Carrageenan-induced edema in mice

Edema was induced in the left hind limb of the mice (n=5) by injecting 0.05 ml of 1% carrageenan solution by the method described by Singh et al. (1986).

Acetic acid induced vascular permeability in mice

Evan's blue (0.2 ml of 0.25% w/v) solution was injected *i. v.* into mice (n=5) 30 min following oral drug treatment (Whittle, 1964). After 15 min, 1 ml/100 g of acetic acid (0.6% v/v) solution was *i. p.* injected, the peritoneal cavity was washed with 5 ml of heparinised saline and the dye content was measured spectrophotometrically.

Cotton pellet-induced granuloma in rats

Autoclaved cotton pellets (50 ± 1 mg) were implanted under each axilla and groin region under ether anaesthesia (Winter and Porter, 1957).

Formaldehyde arthritis in rats

Edema was induced by injecting 0.1 ml of formaldehyde (2% v/v) solution into the left hind paw in groups of 5 rats (Selye, 1949).

Adjuvant-induced developing arthritis in rats

Arthritis was induced by injecting 0.05 ml of 0.5% w/v suspension of killed *Mycobacterium tuberculosis* (Difco) finely homogenised in liquid paraffin into the left hind foot (Newbould, 1963). Paw volume was measured and the percent inhibition was calculated on day 14.

Adjuvant-induced established arthritis in rats

Arthritis was induced in rats as described above. Drug treatment was started on day 14 and terminated on day 28 (Newbould, 1969).

Bovine serum albumin (BSA)-induced arthritis in rabbits

Arthritis was produced in rabbits (n=4) using the method developed by Gall and Gall (1980). Seventeen days after immunization the rabbits were challenged by injecting 0.5 ml of sterile BSA (30%) in saline into the right knee joint. An equal amount of saline was injected into the left knee to serve as the control. Synovial fluid was collected daily up to 28 days for total and differential leucocyte counts (TLC and DLC).

Sodium urate-induced gouty arthritis in dogs

The knee joint of mongeral dogs of either sex (6–9 kg) organized into groups of four were injected with 0.5 ml of sterilized normal saline containing 10 mg sodium urate crystals 1 h after oral drug treatment (Faires et al., 1962). The animals were observed for inflammation of the joint, total leucocyte count and typical three legged gait.

Carrageenan-induced pleurisy in rats

Pleurisy was induced by injecting 0.5 ml of carrageenan (1% w/v) into the pleural cavity of rats organized into groups of 5 (Meacock and Kitchen, 1979).

Effect on serum transaminases in arthritic rats

Established arthritis was produced as described above. BA was orally administered for 2 weeks and at the termina-

tion of study, blood was collected for estimation of serum transaminases (Hanson, 1963).

Effect on gestation, litter size and post-partum bleeding in rats

Female rats organized into groups of 5 were used as described by Aiken (1972) on days 18 to 21 of gestation. The drug was orally administered twice daily. Animals were observed during the gestation period.

Effect on castor oil-induced diarrhea in rats

Rats that were fasted overnight were organized into groups of five and were administered the drug orally. After 1 h, castor oil (1 ml/100 g p. o.) was administered and the animals observed for the onset and character of diarrhea (Awouters et al., 1978).

Ulcerogenic effect in rats

Using Cashin's method (1977), the test drug was administered to rats fasted overnight. The animals were sacrificed 3 h after dosing, their stomachs removed, cut along the lesser curvature and scored according to the arbitrary scale.

Analgesic activity in mice

Analgesic activity was determined in mice organised into groups of 10 using the tail clip method of Bianchi and David (1960) and the acetic acid-induced writhing syndrome (Witkin et al., 1961).

Antipyretic activity in rats and rabbits

Pyrexia was produced in rats by injecting 2 ml of yeast (15% w/v) suspension in gum acacia (2% w/v) (Brownlee, 1937) and in rabbits (n=4) by *i. v.* injecting 0.1 ml of TAB vaccine. Test compounds were administered when pyrexia was maximal. Hourly temperature, were recorded up to 4 h.

Results and discussion

The findings of this study shows BA to possess varying degrees of AIA in dose-related patterns in a variety of acute and chronic test models. In acute tests, BA in a dose range of 50–200 mg/kg administered orally elicited AIA of 26–43% in rats, of 20–34% in mice with carrageenan induced edema, of 21–51% in dextran-induced edema in rats and 18–37% in histamine-induced edema in rats (Fig. 1). The AIA of BA was not affected in adrenalectomised rats, thereby ruling out the possibility of its activation by the pituitary adrenal axis (Fig. 1). This was further supported by

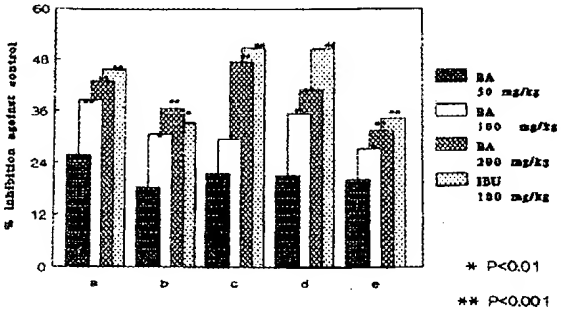

Fig. 1. Anti-inflammatory effect of BA orally administered on edema induced by carrageenan (a), histamine (b), dextran (c), carrageenan in adrenalectomised rats (d) and carrageenan in mice (e). Each value denotes the mean of 5 animals. Level of significance determined by using student's T-test.

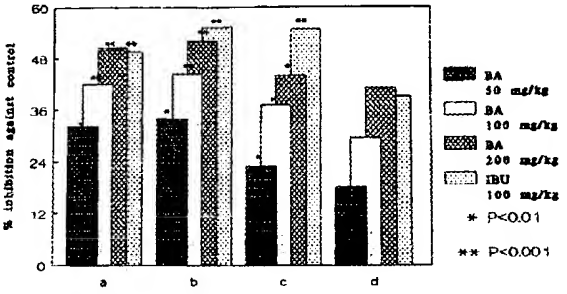

Fig. 2. Dose-related anti-arthritic activity of BA upon oral treatment for: developing adjuvant arthritis (a) and established adjuvant arthritis (b) in rats following injection of 0.05 ml of *Mycobacterium tuberculosis* (0.5% w/v) into the left hind foot; [formaldehyde arthritis (2% v/v formaldehyde) into the hind paw on 1st and 3rd day of experiment (c)] and gouty arthritis (d) induced by injecting 10 mg sodium urate crystals contained in 0.5 ml of sterile normal saline into the left stifle joint of dogs.
Each value represents the mean of 5 rats and 4 dogs. Level of significance determined by using student's T-test.

its weak inhibitory action in cotton pellet-induced granuloma in rats, which is considered to me more sensitive to steroidal type drugs and where NSAIDs show poor activity (DiRosa et al., 1979). Enhanced vascular permeability is a characteristic event in acute inflammation; BA (50–200 mg/kg p. o.) inhibited vascular permeability by 32 to 44%.

In chronic tests using the developing adjuvant polyarthritis, BA in doses of 50–200 mg/kg produced marked anti-arthritic activity of 32 to 50% (Fig. 2). BA also significantly reduced the development of secondary lesions. In similar doses it exerted marked inhibitory action (34–52%) in established adjuvant arthritis in rats, suggesting its possible usefulness as a therapeutic agent. Its reversal of syndromes of established arthritis indicates that it can control the damage caused by immunological mechanisms. The

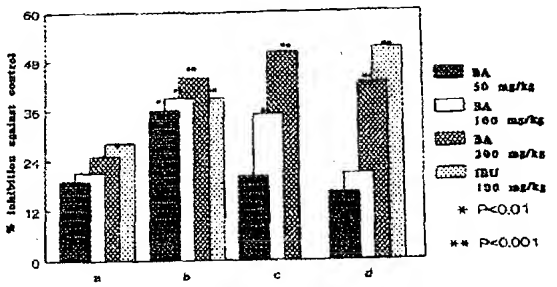

Fig. 3. Inhibitory action of orally administered BA on pleural exudate volume (a), total leucocyte counts (b) in carrageenan induced pleurisy in rats following 0.5 ml injection of carrageenan (1% w/v) into the pleural cavity, total leucocyte counts in BSA induced arthritis in rabbits (c). The animals were challanged with 0.5 ml of 30% BSA in sterile saline into the right knee 17 days after immunization. Synovial fluid was collected on different days with the final collection being made on day 28, and on TLC determined from the aspirated synovial fluid from the stifle joint of gouty arthritis dogs (d).

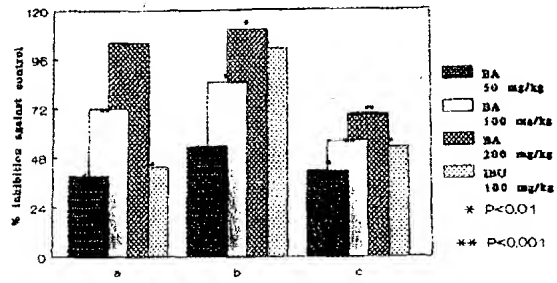

Fig. 4. Inhibitory effect of BA orally administered on arthritis elevated levels of serum glutamic oxaloacetic transaminase (SGOT) (a), serum glutamic pyruvic transaminase (SGPT) (b) and alkaline phosphatase (c).
Each bar represents the mean of 5 rats. Significance different from control determined using the student's T-test.

AIA of BA was further substantiated by their inhibitory action on serum glutamic oxaloacetic transminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase levels enhanced by chronic inflammation in established adjuvant arthritis in rats (Fig. 4). In formaldehyde arthritis in rats, BA (50–200 mg/kg p.o.) displayed AIA in 23–44% of the cases (Fig. 2). Since migration of leucocytes plays an important role in the development of inflammatory conditions, inhibition of their migration might account for part of a drug's anti-inflammatory action. In our study on BSA-induced arthritis in rabbits, treatment with BA in multiple oral doses (25–100 mg/kg) reduced the leucocyte count of in the aspirated synovial fluid (Fig. 3). Single intrapatellar injections of BA (5–20 mg/knee) elicited a similar effect. Similarly administration of BA (50–200 mg/kg p.o.) in sodium urate gouty arthritis in dogs, reduced leucocyte counts in synovial fluid by 16 to 42% (Fig. 3) and lessened the swelling of the stifle joint (Fig. 2). Dogs treated with BA showed moderate to marked improvement in their gait, whereas untreated dogs displayed a typical three-legged walk and evinced pain when made to move.

In the carrageenan-induced pleurisy test in rats, BA markedly reduced exudate volume (19–25%) and TLC by 36–44% (Fig. 3). These inhibitory results of BA on leucocyte migration may be attributed to the inhibition of release or formation of chemotactic factors (Sell, 1980). BA at 100 and 200 mg/kg p.o. lowered pyrexia in rats and rabbits by 1 to 2 °C. BA failed to exhibit any ulcerogenic effect in doses as high as 1000 mg/kg in rats. On the other hand, 200–500 mg/kg of BA administered orally exhibited a protective effect on HCL-alcohol and indomethacin-induced ulcers in rats (unpublished data).

A strong correlation has been reported between the potency of NSAIDs as inhibitors of PGs synthesis and as irritants of the gastrointestinal tract (Boyle et al., 1982; Cashin et al., 1977). BA lacked any ulcerogenic action. Inhibition of PG synthetase is a common mode of inhibitory action in NSAIDs (Vane, 1971). Like other NSAIDs, BA possess prominent anti-inflammatory but weak anti-pyretic activities. The absence of analgesic activity and especially the lack of ulcerogenic effects in the stomachs of tested rats suggests that BA do not act primarily by inhibiting PG synthesis. This is further supported by the fact that unlike other NSAIDs orally administered BA (50–200 mg/kg) failed to prolong the gestation period and parturition time in pregnant rats and did not affect the onset time of castor oil-induced diarrhea in rats – effects that have been attributed to the inhibition of PG synthesis (Aiken, 1972; 1974; Awouters et al., 1978). Using an *in vitro* test system of endogenous arachidonic acid in rat peritoneal neutrophils, Safayhi et al. (1992) reported that BA has a strong inhibitory action on the formation of the 5-lipoxygenase product, leukotriene LTB_4, in a concentration-related manner, thereby supporting our findings. In a pilot clinical trial 60 patients with rheumatoid arthritis demonstrated significant improvement regarding morning stiffness, pain, swelling of various joints, and restored functional activity following 6–8 weeks treatment with BA (Singh et al., 1987).

In conclusion, BA are a new class of NSAID based on a natural source that has a novel mode of inhibitory action on the formation of 5-lipoxygenase product leukotriene (LTB_4). Lacking the ulcerogenic effect of other classical anti-inflammatory drugs, they emerge as unique candidates to be a drug with immense therapeutic value for the treatment of rheumatoid arthritis.

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Original report

Anti-tumor and anti-carcinogenic activities of triterpenoid, β-boswellic acid

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Abstract. Boswellin (BE), a methanol extract of the gum resin exudate of *Boswellia serrata*, contains naturally occurring triterpenoids, β-boswellic acid and its structural related derivatives, has been used as a traditional medicine for the treatment of inflammatory and arthritic diseases. Topical application of BE to the backs of mice markedly inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal proliferation, the number of epidermal cell layers, and tumor promotion in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice. Feeding 0.2% of BE in the diet to CF-1 mice for 10–24 weeks reduced the accumulation of parametrial fat pad weight under the abdomen, and inhibited azoxymethane (AOM)-induced formation of aberrant crypt foci (ACF) by 46%. Addition of pure β-boswellic acid, 3-*O*-acetyl-β-boswellic acid, 11-keto-β-boswellic acid or 3-*O*-acetyl-11-keto-β-boswellic acid (Fig. 1) to human leukemia HL-60 cell culture inhibited DNA synthesis in HL-60 cells in a dose-dependent manner with IC_{50} values ranging from 0.6 to 7.1 μM. These results indicate that β-boswellic acid and its derivatives (the major constituents of Boswellin) have anti-carcinogenic, anti-tumor, and anti-hyperlipidemic activities.

Keywords: Boswellin, triterpenoid, triterpene acid, boswellic acid, cancer prevention

1. Introduction

The plant *Boswellia serrata* grows widely in India. The gum resin exudate of *B. serrata* is collected from the stem of the plant *B. serrata* and is used as a commercial source for the herbal medicine [1]. Boswellin (BE) is an extract of the gum resin of *B. serrata* (a trade name of Sabinsa Corp., NJ). The anti-inflammatory activity and anti-arthritic pain of β-boswellic acids (the major constituents of BE) is due to their ability to inhibit 5-lipoxygenase activity [1–4]. Rats when treated orally with BE and β-boswellic acids in the range of 50–200 mg/kg of body weight showed anti-arthritic activity comparable to phenylbutazone [5]. Treatment of humans or horses with BE or β-boswellic acids resulted in improvement of arthritic conditions [1,5,6]. The gum resin exudate of *B. serrata* also has anti-hyperlipidemic and

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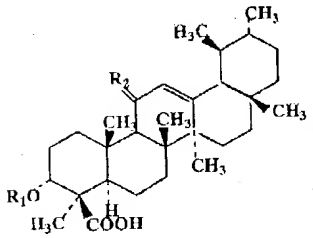

1. R_1=H, R_2=H_2: β-Boswellic acid
2. R_1=Ac, R_2=H_2: 3-*O*-Acetyl-β-boswellic acid
3. R_1=H, R_2=O: 11-Keto-β-boswellic acid
4. R_1=Ac, R_2=O: 3-*O*-Acetyl-11-keto-β-boswellic acid

Fig. 1. Chemical structures of β-boswellic acid and its derivatives.

anti-atherosclerotic activities [7,8]. We now report that topical application of BE inhibited TPA-induced skin inflammation, epidermal proliferation and skin tumor promotion. We also show that BE has anti-hyperlipidemic activity and inhibits AOM-induced formation of ACF (early colon tumor marker) as well as anti-tumor activity of pure boswellic acid and its derivatives.

2. Materials and methods

2.1. Preparation of Boswellin and chemical composition

Oleogum resin exudate of *B. serrata* (100 g) was extract with methanol (200 ml × 3), the methanol evaporated in vacuum to give 45 g of dried extract. The dried extract (30 g) was dissolved in 2% KOH solution (200 ml). The ethyl acetate extract was discarded, and the aqueous solution was neutralized with 2% HCl to pH 6.0, and then extracted with ethyl acetate (5 × 150 ml). The combined ethyl acetate solution was washed with water, and dried with anhydrous Na_2SO_4 overnight, and then evaporated to dryness to produce 18 g of residue (Boswellin, a mixture of boswellic acid and its derivatives). Boswellin contains about 13–18% β-boswellic acid, 11–17% 3-*O*-acetyl-β-boswellic acid, 6–8% 11-keto-β-boswellic acid, and 4–7% 3-*O*-acetyl-11-keto-β-boswellic acid.

2.2. Preparation of pure β-boswellic acid, 3-O-acetyl-β-boswellic acid, 11-keto-β-boswellic acid, 3-O-acetyl-11-keto-β-Boswellic acid.

Further separation and purification of Boswellin to pure boswellic acid and its derivatives as described in our previous publication [9].

2.3. Animals

CD-1 female mice (23–25 days for ear edema experiments, or 6–7 weeks old for skin tumor experiment) were purchased from Charles River Laboratories (Kingston, NY). The mice were kept in our animal facility for at least 1 week before use. Mice were fed with a Purina Laboratory Chow 5001 diet from Ralston-Purina Co. (St. Louis, MO) and water ad libitum and kept on a 12 h light/12 h dark cycle. The dorsal region of each mouse was shaved with electric clippers at least 2 days before treatment with TPA or DMBA. Only mice that did not show signs of hair regrowth were used.

2.4. Quantification of aberrant crypt foci

Female CF-1 mice (5–6 weeks old; 10–30 mice per group) were received s.c. injection of AOM (5, 10, 10, 10 mg/kg) once a week (total 4 injections). The test compounds in the diet are given to mice at 2 weeks before the first AOM injection, during, and continuing until the end of the experiment (initiation + post-initiation period). At 24 weeks after the last dose of AOM injection, the mice were killed and colon (from anus to caecum) was removed, opened longitudinally, rinsed with normal saline solution, and stapled on a plastic sheet. The colon samples were placed in a 10% neutral buffered formalin solution for 24 hours. The entire colon was stained with 0.2% methylene blue dissolved in phosphate buffer saline (PBS) solution for 20 minutes. The whole mount of colon samples were examined in a light microscope. Only ACF meeting the criteria with crypts of increased size with a thicker and deeply stained epithelial lining and an increased pericryptal zone compared with normal crypts were chosen.

2.5. Determination of proliferation of epidermis by bromodeoxyuridine (BrdUr) labeling index

Immunohistochemical staining for BrdUr was performed according to the procedure of the commercial assay kit as described in our previous publication [10].

2.6. Measurement of edema of mouse ears

Measurement of mouse ear edema was done according to the following procedure. Both ears of female CD-1 mice (23–25 days old; 5–6 mice per group) were treated topically with 20 μl acetone, 0.5 nmol TPA in acetone or Boswellin together with 0.5 nmol TPA in acetone. Five hours later the mice were sacrificed by cervical dislocation, and 6-mm (diameter) ear punches biopsies were taken and weighed. The increases in weight of the ear punches were directly proportional to the degree of inflammation.

2.7. Tumor studies on mouse skin

The dorsal region of CD-1 female mice (8 weeks old) were shaved with electric clippers. For studies on the inhibitory effect of topical application of Boswellin on TPA-induced tumor promotion, the mice (30 per group) were treated topically with 200 nmol of 7,12-dimethylbenz[a]anthracene (DMBA) in 100 μl of acetone. A control group of mice received 200 μl of acetone alone. After 1 week the mice were treated topically with 200 μl of acetone, 5 nmol of TPA, or 5 nmol of TPA together with 1.2 or 3.6 mg of Boswellin (BE) in acetone twice weekly for 18 weeks. Skin tumors greater than 1 mm in diameter were counted and recorded every 2 weeks. All skin tumors were examined histopathologically.

3. Results

3.1. Inhibitory effect of topical application of BE on TPA-induced biomarker changes

The possibility that BE could inhibit TPA-dependent inflammation was evaluated by studying the effects of BE on TPA-induced edema of mouse ears. Topical application of 0.06–0.24 mg of BE with 0.5 nmol to the ears of mice inhibited TPA-induced edema by 40–84% (Table 1). BE strongly inhibited TPA-induced proliferation of mouse epidermis as determined by the incorporation of bromodeoxyuridine (BrdUr) into epidermal DNA. Twenty four hours after the last dose of topical application of 5 nmol of TPA once a day for 2 days resulted in a 43% BrdUr labeling index. Topical application of 3.6 mg of BE together with 5 nmol of TPA once a day for 2 days results in a decrease BrdUr labeling index to 8.3%, Thus BE inhibited TPA-induced epidermal proliferation by 81% at 3.6 mg.

Table 1
Effect of boswellic acids and Boswellin extract on TPA-induced edema of mouse ears

Treatment	Weight per ear punches (mg/punch)	Percent inhibition (%)
Acetone	6.4 ± 0.16	–
TPA	13.9 ± 0.45	–
TPA + Boswellin Ext (0.06 mg)	10.9 ± 0.84	40
TPA + Boswellin Ext (0.12 mg)	8.4 ± 0.56	75
TPA + Boswellin Ext (0.24 mg)	7.6 ± 0.10	84

Female CD-1 mice (23–25 days; 5 mice for group 2, 4 mice for all other group) were treated topically 20 μl acetone, 0.5 nmol TPA or TPA and various doses of boswellin extract (BE) in 20 μl acetone. Five hours later, the mice were killed and ear punches were weighed. Data are represented as means ± SE.

3.2. *Inhibitory effect of topical application of BE on TPA-induced tumor promotion in the epidermis of mice previously initiated with DMBA*

BE strongly inhibited TPA-induced skin tumor promotion in the epidermis of female CD-1 mice previously treated with DMBA. Female CD-1 mice initiated with a single dose of 200 nmol DMBA and promoted with 5 nmol of TPA twice weekly for 16 weeks developed an average of 15.8 skin tumors per mouse and 90% of the mice had skin tumors. Topical application of 5 nmol TPA together with 1.2 or 3.6 mg of BE for 16 weeks reduced the number of skin tumors per mouse by 87 and 99%, respectively. The percentage of mice with skin tumor was decreased by 59 or 92%, when topically applied with 1.2 or 3.6 mg of BE together with 5 nmol of TPA twice weekly for 16 weeks. BE treatment delayed the appearance of the first skin tumor. The latent time for 1.2 mg of BE treatment was 4 weeks and was greater than 8 weeks with 3.6 mg of BE treatment. These result suggest that BE is a potent inhibitor of TPA-induced skin tumor promotion on mouse skin.

3.3. *Effect of oral administration of BE in the diet on the accumulation of parametrial fat pad under abdomen*

Oral administration of 0.2% BE in the diet to female CF-1 mice for 11 weeks reduced the accumulation of parametrial fat pad under abdomen in CF-1 mice. Feeding with Western style diet to female CF-1 mice for 11 weeks induced the weight accumulation of the parametrial fat pad to 1.64 g. Feeding 0.2% BE in Western diet for 11 weeks resulted parametrial fat pad 0.91 g. The result indicate feeding BE diet decreased accumulation of parametrial fat pad by 46%.

3.4. *Effect of dietary BE on azoxymethane (AOM)-induced formation of aberrant crypt foci in colon epithelium*

Female CF-1 mice received AOM (5, 10, 10, 10 mg AOM/Kg body weight) at 6 weeks of age once every 4 days and AOM (10 mg)/kg body weight once at 24 weeks. The mice were killed at 35 weeks after the first dose of AOM. The mice received AIN 76A diet or 0.2% BE in AIN 76A diet at 2 weeks before the first dose of AOM, and continued until the end of the experiment. In the control diet group, the average number of aberrant crypt foci per colon was 5.2, and the average of number aberrant crypts per colon was 37. The average number of ACF per colon in mice fed with 0.2% BE in the diet was 3.1 (inhibition of 40%). The average of AC per colon in fed with 0.2% BE in the diet was 6.8 AC per colon

Table 2
Effect of dietary bowellin (BE) on azoxymethane (AOM)-induced formation of aberrant crypt foci (ACF) in CF-1 mice

	Positive control	0.2% BE	0.5% BE
ACF/colon	5.2 ± 1.2	3.1 ± 1.4 (40%)	3.3 ± 1.4 (37%)
AC/colon	37 ± 5.9	6.8 ± 1.1 (82%)	8.8 ± 2.5 (76%)

Female CF-1 mice received AOM (5, 10, 10, 10 mg AOM/Kg) at 6 weeks of age once every 4 days and AOM (10 mg/Kg) once at 24 weeks after the first dose of AOM. The mice received AIN 76A diet or test compound in AIN 76A diet at 2 weeks before the first dose of AOM, and continuing until the end of the experiment. The data are expressed as the mean ± SE. Data in parentheses are % inhibition.

Table 3
The effect of β-boswellic acid and its derivatives on the synthesis of DNA in human leukemia HL-60 cells

Compound	$IC_{50}(\mu M)$
1. β-Boswellic acid	3.7
2. 3-*O*-Acetyl-β-boswellic acid	1.4
3. 11-Keto-β-boswellic acid	0.9
4. 3-*O*-Acetyl-11-keto-β-boswellic acid	0.6

(82% inhibition see Table 2). The results indicated that dietary BE strongly inhibited AOM-induced formation of the number of ACF per colon and AOM-induced progression from early stage to late stage of ACF.

3.5. Inhibitory effect of pure β-boswellic acid and its pure derivatives on the synthesis of DNA in HL-60 cells

All 4 pure triterpene acids, β-boswellic acid, 3-*O*-acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and 3-*O*-acetyl-11-keto-β-boswellic acid inhibited DNA synthesis on human leukemia HL-60 cells in a dose-dependent manner with IC_{50} values ranging from 0.6 to 7.1 μM, among them compound 4,3-*O*-acetyl-11-keto-β-boswellic acid induced the most pronounced inhibitory effects on DNA synthesis with IC_{50} value of 0.9 μM (Table 3).

4. Discussion

The results of the present study demonstrate that topical application of BE inhibits TPA-induced mouse ear edema, TPA-induced epidermal proliferation, TPA-induced increases in the number of epidermal cell layers, and TPA-induced skin tumor promotion in CD-1 mice. Since β-boswellic acid is able to inhibit 5-lipoxygenase activity [2–4]. The anti-inflammatory, anti-tumor promoting and anti-arthritic activities may be due to its capability of inhibiting lipoxygenase activity [4–6]. All 4 pure β-boswellic acids inhibit DNA synthesis in human leukemia HL-60 cells in a dose-dependent manner with IC_{50} values ranging from 0.6 to 7.1 μM, among them 3-*O*-acetyl-11-keto-β-boswellic acid induced the most pronounced inhibitory effects on DNA synthesis with IC_{50} value of 0.6 μM [9], perhaps due to induction of differentiation and apoptosis in HL-60 cells by boswellic acid acetate [11]. In addition, feeding BE in

the diet to CF-1 mice also inhibits the accumulation of parametrial fat pad weight under abdomen, and inhibits AOM-induced formation of AFC in mouse colon epithelium. BE, pure β-boswellic acid and its derivatives may be proved to be broad cancer chemopreventive agents as well as anti-hyperlipidemic agents.

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